

There are more than 80,000 chemicals used today worldwide, and the impact of many of these chemicals on human health is largely unknown. While relatively few such chemicals are thought to pose a significant risk to human health, the safeguarding of public health depends on identifying the effects of these chemicals and the levels of exposure at which they become potentially harmful to humans.

In order to address these issues, the National Toxicology Program (NTP) was established by the U.S. federal government in 1978. In its 20 years of existence, the NTP has become the world's leader in designing, conducting, and interpreting various types of assays for chemical toxicity. "The NTP is not only a national resource, but an international resource as well, containing some of the best scientific thinking coupled with laboratory ability, allowing us to understand the role of chemicals—whether they be harmful or helpful," says Linda Rosenstock, director of the Centers for Disease Control and Prevention's (CDC) National Institute for Occupational Safety and Health (NIOSH).

The NTP was created as a cooperative effort to coordinate toxicological testing programs within the Department of Health and Human Services (DHHS) in response to the needs of various agencies for toxicity data. The NIEHS was designated as the focal point for the establishment of the NTP, which comprises components of three agencies—the NIEHS, the NIOSH, and the Food and Drug Administration's (FDA)

National Center for Toxicological Research (NCTR). The National Cancer Institute (NCI) was a charter agency, and remains active on the NTP Executive Committee, which provides program oversight. Through his position as director of the NIEHS, Kenneth Olden is also the director of the NTP. Says Olden, "Integration of NIH basic science with efforts to evaluate toxicological data is essential to solving the problems of adverse environmental health exposures." The committee is made up of the heads of several DHHS agencies—the NIEHS, the NCI, the Agency for Toxic Substances and Disease Registry (ATSDR), the CDC's National Center for Environmental Health (NCEH), NIOSH, and the FDA—as well as non-DHHS agencies, including the Occupational Safety and Health Administration (OSHA), the EPA, and the Consumer Product Safety Commission.

The goals of the NTP are to provide toxicological evaluations of substances of public health concern, to develop and validate improved testing methods, to develop approaches and generate data to strengthen the science base for risk assessments, and to communicate with all stakeholders, including government, industry, academia, the environmental community, and the public.

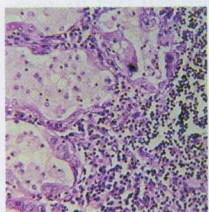
Public Health Policy

The scientific data generated by the NTP are used in the establishment of regulatory guidelines, such as safe occupational exposure levels, and as a basis for public health decisions made by state and federal agencies, as well as private organizations. The NTP strives to meet the needs of the groups that use its data. "We feel it's important to generate the types of data that are consistent with the guidelines of the regulatory agencies, as well as data that contribute to an understanding of how a chemical or physical agent produces a biological effect," says George Lucier, director of the NIEHS's Environmental Toxicology Program (ETP), which administers the NTP.

Over the last 20 years, the role of the NTP has evolved beyond producing data to include interpretation of those data. "It's not good enough for us to just generate the data; we also work to translate the data for regulatory agencies," says Lucier. "Our link to public health policy needs to be direct and clear. Regulatory decisions can only be as good as the science on which they are based."

"We have a very interactive relationship with regulatory agencies," adds John Bucher, deputy director of the ETP. He says the NTP is now working with more agencies during the design of toxicity studies, which should result in findings that are directly relevant to the questions facing the agencies. Ultimately, Bucher says, this means that "there is a better chance that the results we get are used appropriately in public health decisions."

The emerging field of mechanism-based toxicology uses molecular biology tools to characterize interactions of chemicals with critical target genes. By understanding the sequences of molecular and biological events that occur in order for a chemical to produce a toxic effect, researchers can create more specific and sensitive tests for use in risk assessments that are also less expensive because they require the use of fewer or no animals. Examples of mechanism-based toxicology include methods for identifying receptor-mediated toxicants, molecular screening strategies, use of transgenic animals, and development of alternative or complementary *in vivo* tests to use with the rodent bioassays. The NTP strives to provide the necessary science base for regulatory agencies to use in assessments. Roger McClellan, president of the Chemical Industry Institute of Toxicology in Research Triangle Park, North Carolina, says the NTP has also evolved from having a primary emphasis on testing to a much better balance between testing and research on understanding the mechanisms of action of chemical agents as well as the relevance of the test findings for assessing human risk. NTP researchers have made significant progress in achieving this balance in several distinct and complementary research areas.



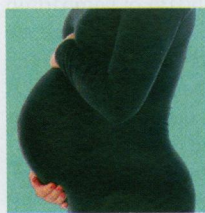
Carcinogenicity. In the last 20 years, the NTP has tested nearly 500 chemicals for carcinogenicity and has identified many important potential human carcinogens, including dioxin, benzene, methylene chloride, polychlorinated biphenyls (PCBs), phenolphthalein, and ozone.

One of the most notable contributions of the NTP to public health policy has been the publication of the *Report on Carcinogens*, which lists substances to which a significant number of people residing in the United States are exposed as either “known to be a human carcinogen” or “reasonably anticipated to be a human carcinogen.” Since it was first published in 1980 (the report has been updated several times since then, most recently in 1998), the *Report on Carcinogens* has been a valuable resource for regulatory agencies, as well as industry and public interest groups. Says Lucier, “Our role is to provide information that’s credible, objective, and enables public health officials to make good decisions.”

In 1995, a major revision of the criteria for listing chemicals or substances in the report allowed a broader consideration of mechanistic data. Due to this revision, Rosenstock says the process for nominating

and listing chemicals is now better defined and allows for greater openness and input, thereby increasing the report’s credibility. Critics, however, feel that the reporting process needs still further revision. McClellan calls the report “an overly simplistic list of potential hazards that confuses rather than enlightens the public.” He says he would like to see the NTP move beyond producing lists and continue to focus more attention on understanding and evaluating human risk. NTP leaders maintain that the list format is mandated by Congress in the Public Health Service Act, and the list is vital information. Says Carl Barrett, scientific director of the NIEHS, “Although the NIEHS realizes that different chemicals have different levels of risk, it is important to generate a list of chemicals that are known or reasonably anticipated human carcinogens. This list is used by many groups including regulatory agencies, industry, and the public. In fact, few of the chemicals tested by the NTP are listed in the *Report on Carcinogens* because most do not meet the criteria for listing as a human risk. Many of the efforts of the NTP are now focused on improving the understanding of risks to humans.”

While cancer is the best known and most studied adverse human health impact of toxic chemicals, many chemicals affect human health in other ways, for example, by causing damage to the reproductive and immune systems. Over the years, the NTP has devoted considerable resources to studying the impact of chemicals on human health beyond cancer, and has made significant advancements in this field. “There has been a greater emphasis within the NTP on noncancer endpoints, and this has been done without abandoning carcinogenicity,” says Barry Johnson, director of the ATSDR. “It was absolutely vital that that change occur. Looking at non-cancer endpoints is extremely important, and I commend the NTP for providing leadership to look beyond cancer.”



Reproductive and developmental toxicology. One of the most controversial areas of toxicological research examines the impact of chemicals on the reproductive system and human development. The NIEHS was the first federal agency to recognize that environmental hormones could pose a public health concern. In 1977, the NIEHS hosted one of the first conferences on environmental estrogens.

Research conducted by the NIEHS and the NTP has found that chemicals that possess hormonal action can alter normal human development, causing not only gross

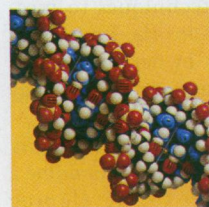
malformations, but also subtle changes that may not be apparent for many years. Ron Miller, project manager of the environment, health, and safety division of Dow Chemical, says the NTP has made important contributions to the field of endocrine disruptor research, but has focused too much attention on man-made chemicals. “The NTP should expand research to include all potential endocrine disruptors—not just chemicals, but natural substances and even habitat destruction,” he says.

Miller commends NTP leaders for forging partnerships between public and private organizations over the years, and hopes the NTP will collaborate with other groups in examining endocrine disruptors. “There are clear opportunities for partnerships between public and private groups as we move forward in the area of endocrine disruptors, particularly in the validation of screening assays and in low-dose research,” Miller says.

“The NTP is definitely going to be instrumental in overcoming the obstacles and blinders that we’ve had with traditional toxicology,” says toxicologist Theo Colborn of the World Wildlife Fund. “The NTP is showing a vision and leadership concerning how endocrine disruptors [affect human health, and] in finding and using tools to detect chemicals with these insidious effects.”

The NTP is also focusing on the effects of toxic chemicals on growth and development in children. NTP researchers found in one study that transplacental exposure to PCBs and DDE (a metabolite of DDT) produces small but persistent delays in motor development detectable from birth to the age of two years. A second study showed that children who were exposed transplacentally to PCBs and polychlorinated dibenzofurans after their mothers ate contaminated cooking oil developed ectodermal defects, persistent developmental delay, and disordered behavior.

In order to shed more light on these issues, the NTP spearheaded the development of the Center for Evaluation of Risks to Human Reproduction (see NIEHS News, p. A480). For the purposes of the center, reproduction is broadly defined to include effects on fertility, the genetic integrity of germ cells, the developing fetus, and early postnatal development. Anyone, including the public, will be allowed to nominate agents to be evaluated, and reports



on the activities of the center will be available through an Internet site.

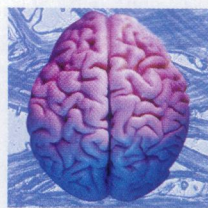
Genetic toxicology. The NTP created and continues to develop an extensive

database comparing results of widely used genotoxicity assays, which has proved to be an invaluable resource in the field. Of the database, which was begun in 1980, Ray Tennant, chief of the Laboratory of Environmental Carcinogenesis and Mutagenesis at the NIEHS, says, "It is a unique, multiassay, genetic toxicology database . . . [and] remains an important contribution to the field."

The NTP also conducted the first comprehensive evaluation of genetic toxicology assays. The results, published in the 22 May 1987 issue of *Science*, showed the need for a different approach in designing assays for detecting carcinogens or mutagens. Says Tennant, "The paper had a big impact worldwide. It changed the way investigators thought about the problem of developing alternative assays."

In 1990, the NTP initiated the Predictive Toxicology Evaluation Project, an effort to utilize chemical structure and other parameters to predict the outcome of bioassays. The first complete listing of results, published in the October 1996 issue of *EHPS*, identified specific deficiencies in the capability of various methods to identify carcinogens. The project is currently in a second phase and will be the subject of a workshop in 1999.

Genetic toxicology researchers at the NTP have also begun to develop alternative *in vivo* tests for predicting cancer. In 1988, the NTP began toxicology and carcinogenicity studies in transgenic mice and published a paper in the July–August 1995 issue of *EHP* that proposed the use of specific transgenic mouse models to identify potential carcinogens. The recommendations of the paper led to the formation of a consortium made up of the NTP, U.S. and Dutch government bodies, pharmaceutical companies, and research groups that is working on a project to further investigate the use of transgenic animals (see **Commentary** by Bucher, p. 619). The project is being coordinated by the Washington, DC-based International Life Sciences Institute, a nonprofit organization that conducts health research.



environmental factors in nervous system damage," says Jean Harry, neurotoxicology group leader in the ETP.

In 1977, a neurotoxicology laboratory was established at the NIEHS to examine a number of approaches for developing

methods for detecting and characterizing neurotoxicity of chemicals. This research resulted in the development of the NIEHS Neurobehavioral Test Battery and components of the Functional Observational Screening Battery currently used in regulatory testing. The Neurobehavioral Test Battery represents a systematic approach to screening compounds, using semiautomated test systems to quantify chemically induced alterations in various nervous system components.

The laboratory, which is now headed by Harry, is working closely with the EPA to develop a battery of cellular and molecular markers to detect the potential for chemicals to act as developmental neurotoxicants in humans.



Inhalation toxicology. The NTP contributed significantly to the understanding of inhalation toxicology with a series of studies on methyl isocyanate (MIC). The studies were prompted by the 1984 release of MIC from a pesticide manufacturing plant in Bhopal, India, which caused extensive injuries and deaths. In 1985, the U.S. Department of State and the World Health Organization requested that studies be conducted to provide basic toxicology information on MIC. The results of the studies, which were published in the June 1987 issue of *EHPS*, clearly characterized pulmonary and other effects in rodents that could be used to predict the long-term consequences of exposure to MIC in humans.

Among other current projects, the NTP is investigating the effects of exposure to fibers. Over the last 20 years, asbestos inhalation has contributed to the deaths of between 250,000 and 400,000 people. NTP and NIEHS scientists, after extensive research in this area, are currently seeking to use asbestos risk as a standard of comparison for a wide range of fibers to which people are exposed. The NTP is currently developing strategies with a number of other federal agencies for evaluating dose–response relationships for asbestos and other fibers.



Immunotoxicology. In the 1980s, NTP senior investigators participated in an interlaboratory effort that established a testing battery to assess chemically induced immunotoxicity, the results of which were published in the January 1988 issue of *Fundamental and Applied Toxicology*. The article outlined a panel of tests for detecting

immune alterations in rodents following chemical or drug exposure. "This paper standardized the methodology and gave a frame of reference for immunotoxicology testing," says Dori Germolec, group leader of the NTP's Laboratory of Environmental Immunology. Germolec says the article is one of the most frequently referenced papers in immunotoxicology.

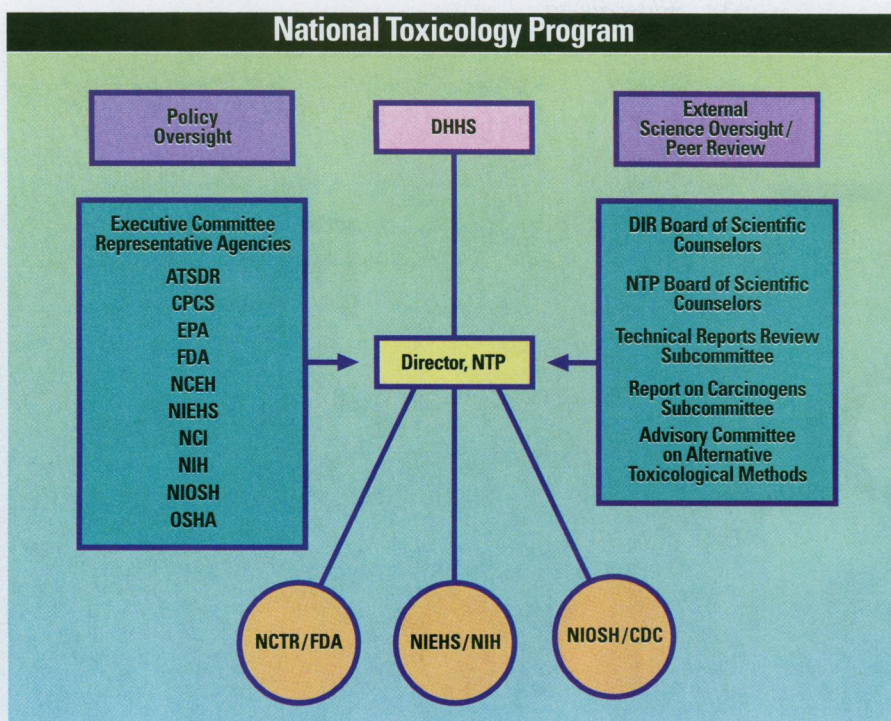
The NTP also published one of the first scientific studies to examine the sensitivity and predictability of specific tests and combinations of individual tests for immune function for use in risk assessment. The results of the study, published in the February 1992 issue of *Fundamental and Applied Toxicology*, showed that combining single tests to measure multiple components of the immune system increases predictability. The results have had a significant influence on how immunotoxicology data are used for risk assessment purposes, and on the development of regulatory guidelines to assess the potential immunotoxicity of chemicals and drugs, according to Germolec.

The NTP has taken part in several interagency efforts to examine health effects in a number of worker populations that are exposed to compounds with the potential to modulate the immune system. For example, the NTP teamed up with NIOSH to investigate occupational asthma in workers at an egg-processing facility, and found there was a significant association between exposure to egg proteins and respiratory symptoms, hypersensitivity, and asthma. The NTP is currently working with NIOSH to examine latex allergies in health care workers.



Risk assessment methodologies. Over the last 20 years, the NTP has been at the forefront in studying risk assessment methodologies. The NTP has developed mathematical risk assessment models, which are necessary for quantifying the sequence of events that starts with chemical exposure and ends with toxicity. The NTP has also produced biologically based models that allow researchers to link a broad array of experimental findings in a way that is biologically logical and eventually useful for risk assessment methods including dose–response relationships, species comparisons, and interindividual variation.

Among the complete models that have been developed by the NTP are the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 1,3-butadiene models, which include the best characterizations available of the pharmacological and biochemical effects of



A group effort. The National Toxicology Program, established in 1978, comprises researchers from three federal agencies—the FDA, the NIEHS (where the program is housed), and NIOSH—through specific scientific offices at each of these agencies. Oversight for the program is provided for policy issues by the directors of 10 federal agencies and for science/peer review by a mix of federal, academic, industrial, and public interest science experts. The director of the NTP is also the director of the NIEHS and reports to the Department of Health and Human Services.

these compounds. A significant accomplishment by the NTP was a restructuring of toxicokinetics, which involved focusing more on quantitative (rather than just qualitative) endpoints to reflect the needs of the risk assessment community.

Current areas of research include mechanistically based cancer models, which are being developed for and applied to NTP data, and predictive toxicology, which is a new area of study referring to the use of physico-chemical parameters in concert with biological data to predict human toxicity and quantify dose-response relationships for that toxicity.

The NTP is striving to strongly link its efforts in risk assessment methodology to mechanism-based toxicology, which offers opportunities to improve priority setting, use mechanistic information to establish safety or risk, clarify dose-response relationships in the low dose region, select the most appropriate experimental systems for estimating risks, and develop science-based models for sensitive subpopulations based on age, gender, and genetic predisposition.

Currently, a major interagency initiative is being developed in exposure assessment—frequently the weakest link in risk assessments—to quantify the body burdens of chemicals to which people are exposed in the environment, workplace, and home (see

Commentary by Lucier and Schecter, p. 623). Chris Portier, chief of the NIEHS Laboratory of Computational Biology and Risk Analysis, says the NTP will do “a lot more work on basic underlying biology to develop models that are easily transportable from one environmental hazard to the next.”

On the Research Horizon

Other current NTP research interests include studying the human health effects of exposure to electric and magnetic fields, conducting toxicological evaluations of pharmaceutical agents, and examining the toxic properties of natural products such as phyto- and fungal estrogens and fumonisin, a mycotoxin that grows on food. NTP researchers are also looking at relationships between ecological events and human health, such as the health effects of exposure to *Pfiesteria piscicida* (a dinoflagellate that for unknown reasons kills fish and has been shown to be neurotoxic to some humans) and fish-kill waters, and how the prevalence of malformed frogs in wetlands in Minnesota and many other states may indicate the presence of human disease.

The NTP also plans to further study chemical mixtures and orphan chemicals (drugs that are produced in limited amounts or chemicals that are no longer in production). Little is known about the impact of

chemical mixtures on human health, and the NTP plans to devote more resources to investigate mixtures to which humans are commonly exposed, such as asphalt. Johnson says the NTP has already demonstrated “laudable research and leadership” in examining these research topics.

As mandated by a federal initiative, the NTP has developed the Center for the Evaluation of Alternative Toxicological Methods to provide operational support for the newly established Interagency Coordinating Committee on the Validation of Alternative Methods (see NIEHS News, p. A480). The committee will work to facilitate cross-agency communication and coordination on issues relating to validation, acceptance, and national-international harmonization of toxicological test methods.

The NTP and the NIEHS are also working with the NCTR to develop the government’s first phototoxicity laboratory. The laboratory will allow researchers to examine how simulated sunlight impacts skin and skin products such as alpha hydroxy acids. “This laboratory will provide new capabilities that will offer a unique opportunity for us to be involved in a new kind of research,” says Bernard Schwetz, director of the NCTR. “We are addressing a public health concern that has not been adequately addressed before.”

On the international level, the NTP plans to pursue collaboration in areas such as the universal harmonization of test methods. “We make extensive use of the NTP’s work,” says Maged Younes, chief of risk assessment and methodologies with the International Programme on Chemical Safety. “NTP data are an important component of our activities, and we envisage more interaction with the NTP in the future in terms of validating new testing strategies. We see this as an area where cooperation can be increased.”

Looking forward, NTP leaders say they will continue to ensure that their research remains on the cutting edge of science. “The NTP has been extremely forward-looking in recognizing the new science that comes along and in moving the program in that direction—carefully and with rigor, so that it’s solidly based,” says Jeanette Wiltse, director of the Health and Ecological Criteria Division in the EPA’s Office of Water. Adds Colborn, “The NTP does very fine work. I’m watching closely as the NTP takes new knowledge forward to make the world a safer place to live.”

Brandy E. Fisher